REMARKS/ARGUMENTS

In response to the Office Action of September 9, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claim 1 has been amended. Claims 2-35 have been cancelled. New claims 36-43 have been added. Claim 1 is withdrawn from consideration. It is understood that claim 1, drawn to a non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. Claims 1 and 36-43 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 21.

The description of the PCT reference at page 4, beginning at line 19 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

In the paragraph at page 6, beginning at line 5, a punctuation error was corrected at line 13.

The "Description of the Figures" section has been amended to add sequence identification numbers for the peptide sequences disclosed therein and to correct grammatical errors. This section has also been amended for consistency of language in the figure descriptions.

The paragraph at page 21, beginning at line 7, has been amended to correct typographical errors.

The protocol at page 21, beginning at line 12, has been amended to correct typographical errors and to properly identify trademark names by capitalization. The title of the protocol was in bold type in the specification as originally filed and does not represent text amended herein.

The paragraph at page 22, beginning at line 2, has been amended to properly identify trademark names by capitalization.

The protocol at page 22, beginning at line 19, has been amended to properly identify trademark names by capitalization.The title of the protocol was in bold type in the specification as originally filed and does not represent text amended herein, with the exception of the capitalization of the trademark name, SEPHAROSE.

The protocol at page 24, beginning at line 1, has been amended to correct typographical errors and to properly identify trademark names by capitalization. The title of the protocol was in bold type

in the specification as originally filed and does not represent text amended herein.

The paragraph at page 24, beginning at line 15, has been amended to properly identify trademark names by capitalization.

The paragraph at page 27, beginning at line 6, has been amended to properly identify trademark names by capitalization.

The paragraph at page 27, beginning at line 17, has been amended to add a sequence identification number to the amino acid sequence disclosed therein.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 28, line 17 in order to provide explicit support for cerebrospinal fluid as recited in claim 38. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to specifically claim the biopolymer marker (SEQ ID NO:1) and to clearly indicate that the claimed marker is isolated from its natural state by the methods described

herein (see, for example, the instant specification at page 31, lines 9-12). Claim 1 has also been amended to indicate that the claimed marker consists of SEQ ID NO:1. The phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to the specific peptide of SEQ ID NO:1.

Claim 1 has also been amended to indicate that SEQ ID NO:1 evidences a link to myocardial infarction. This amendment is supported by the specification as originally filed; page 17, lines 11-14, discloses that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer markers which evidence a link to at least one specific disease state and page 27, line 17 to page 28, line 2 identifies SEQ ID NO:1 as a biopolymer (a fragment of complement component 3)related to the specific disease, myocardial infarction.

No new matter has been added by the addition of new claims 36-43. New claims 36-43 are drawn to methods and kits and are thus still within the scope of the elected invention (Group II). The subject matter of new claims 36-43 corresponds to the subject matter of cancelled claims 2-35. The above additions to the claims also find basis in the original disclosure at page 12, lines 2-12; page 17, lines 7-14; page 18, lines 5-7; page 27, line 17 to page

28, line 2 and Figures 1 and 2. The methods of claims 36-40 are described in detail at pages 20-27. The Surface Enhanced Laser Desorption Ionization (SELDI) mass spectrometric technique is disclosed throughout the instant specification as originally filed; for example, at page 12, lines 2-12. Page 28,line 11 to page 29,line 7 refers to the use of various types of samples and their measurement. The use of unfractionated body fluids and tissue samples in chromatography is discussed at page 11, lines 1-9. Figure 1 shows data derived when using the claimed method on samples obtained from a human patient. Figure 2 shows the characteristic spectrometric profile of the claimed marker (SEQ ID NO:1, the 1562 dalton marker). Page 28, line 3 to page 33, line 2 describes kits and their contents contemplated for use with the claimed methods. Labeling of antibodies and their immobilization on solid supports is specifically discussed at page 32, line 10 to page 33, line 2. It is clear from these specific recitations and from the description of methods utilized that the methods and types of kits were fully contemplated by the inventors at the time of filing and were enabled by virtue of the disclosure as originally filed.

Information Disclosure Statements

The Examiner has pointed out that the listing of references in the specification is not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office, and MPEP 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Thus, the Examiner indicates that unless the Examiner on PTO-892 form or Applicant on PTO-1449 form has cited the references they have not been considered.

The Examiner notes an Information Disclosure Statement filed on August 13, 2001 in paper #5 that has not been found in the application. The Examiner invites Applicants to re-submit the IDS for consideration.

Applicants have no record of an Information Disclosure Statement filed on August 13, 2001 in the instant application.

The Examiner indicates that the Information Disclosure Statements filed on January 31, 2002 and December 9, 2002 have been considered as to the merits prior to the first action.

The references cited within the specification but not included in the above-mentioned Information Disclosure Statements provide general information relating to background information and/or the state of the art, but were not deemed pertinent to the

patentability of the claimed invention.

Drawings

The Examiner notes that the application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

The drawings stand objected to under 37 CFR 1.821(a)(1) and (a)(2) because the graph contains a sequence, which has not been identified appropriately. The sequence must include a sequence identification number. The Examiner requires submission of new formal drawings including SEQ ID NO:1.

Applicants respectfully submit that it is acceptable to include sequence identification numbers for sequences disclosed in the figures in the Brief Description of the Drawings section of the specification; see MPEP 2422.02.

The Brief Description of the Drawings at page 19 of the instant specification has been amended herein to include the sequence identification number (SEQ ID NO:1) for the amino acid sequence disclosed in Figures 1 and 2.

Accordingly, Applicants respectfully submit that the drawings are now in compliance with 37 CFR 1.821(a)(1) and (a)(2) and thus, respectfully request that the objection to the drawings be

withdrawn.

Sequence Compliance

The Examiner asserts that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). The Examiner notes that the application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The Examiner asserts that the disclosure contains sequences that have not been appropriately identified by sequence identification numbers, see page 27 and figures.

The Examiner has requested that Applicant return a copy of the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures with the Response to the Office Action mailed on September 9, 2003; however, Applicants note that no such Notice (form PTO-1661) was attached to the Office Action.

The paragraph at page 27, beginning at line 17 was previously amended in a Preliminary Amendment filed on April 23, 2002 (a second copy of this Preliminary Amendment was filed on November 18,

2002) to add a sequence identification number for the amino acid sequence disclosed therein. This amendment has been repeated herein to insure entry.

The Brief Description of the Drawings at page 19 of the instant specification has been amended herein to include the sequence identification number (SEQ ID NO:1) for the amino acid sequence disclosed in Figures 1 and 2.

Applicants respectfully submit that the instant application is now in compliance with the sequence requirements of 37 CFR 1.821-1.825. However, should the Sequence List (paper and disk copies) not be found fully in compliance with all requirements, Applicants respectfully request prompt notice by telephone in order to accomplish expedited correction within the term allotted.

Objections to the Specification

The Examiner notes that the specification has not been checked to the extent necessary to determine the presence of all possible minor errors and requests applicants' cooperation in correcting any errors of which applicant may become aware of in the specification.

The Examiner points out a typographical error at page 6, line 13, in which parentheses were not closed in the text. The instant specification has been amended to correct this and other similar kinds of errors.

The Examiner notes the use of trademarks in the application (i.e. SEPHAROSE at page 22, line 21 and Amicon at page 27, line 8) which should be capitalized wherever they appear and be accompanied by the generic terminology. The Examiner further notes that although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Applicants have amended the specification herein to properly identify trademark names (AMICON, SEPHAROSE, TRITON, TRIS and EPPENDORF).

The Examiner points out guidelines for the proper language and format of an abstract of a patent application and objects to the abstract of the instant application as it recites the legal phraseology "said".

The abstract of the instant application has been amended herein to remove the legal phraseology "said".

The Examiner has objected to the specification for the alleged improper incorporation of essential material (at page 33, lines 3-8) into the specification by reference to a foreign application or patent, or to a publication.

According to MPEP 608.01(p), "essential" material is defined as; 1)necessary to describe the invention, 2) necessary to provide

an enabling disclosure and 3) necessary to describe the best mode. "Non-essential" material is defined as material used to indicate the background of the invention and the state of the art. Non-essential material may be incorporated by reference into a specification.

The statement at page 33 is intended to include background information and references pertaining to the state of the art. Thus, such material can properly be referred to as "non-essential" material.

Accordingly, Applicants respectfully submit that the text at page 33, lines 3-8 of the instant specification is a proper incorporation by reference of non-essential material.

Applicants have addressed all of the Examiner's objections and respectfully request that the objections to the specification now be withdrawn.

Objection to the Claims

Claims 3-9, 18-28 and 33-35, as presented on November 18, 2002, stand objected to for the following alleged informality: The claims refer to the biopolymer of claim 1. Although acceptable, the claims would be clearer if they were written to include SEQ ID NO:1. This would eliminate ambiguity during prosecution. The Examiner requests that SEQ ID NO:1 be added to independent claims

3, 18, 33, 34 and 35.

The independent claims 3, 18, 33, 34 and 35 have been cancelled herein. All of the remaining pending claims recite the term "SEQ ID NO:1" and do not refer to the biopolymer of claim 1.

Applicants have now addressed the Examiner's objection and respectfully request that the objection to the claims be withdrawn.

Rejections under 35 USC 112, second paragraph

Claims 3-9, 18-28 and 33-35, as presented on November 18, 2002, stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The Examiner alleges that in claims 3-5 the terms "evidencing" and "characterizing" are vague and indefinite because it is not clear as to what "evidencing" and "characterizing" encompasses. The Examiner suggests that if the method merely detects myocardial infarction or congestive heart failure via a biopolymer marker (defined in the disclosure) that the phrases are replaced with "detecting" in order to clarify Applicant's intended meaning.

Claims 3-5 have been cancelled herein. None of the remaining pending claims recite the terms "evidencing" or "characterizing".

B. The Examiner alleges that claims 3-9 are vague and indefinite because it is not clear as to what the biopolymer marker or analyte will entail. As cited the method is directed to a correlation of the unknown biopolymer with SEQ ID NO:1, however it is not clear as to what the final correlation will be. For example, does the biopolymer correlate to SEQ ID NO:1 as a 100% match, 90% match, etc. The Examiner indicates that appropriate correction is required.

Claims 3-9 have been cancelled herein. New claim 36 clearly indicates that the mass spectrum profile of SEQ ID NO:1 is compared to the mass spectrum profiles of peptides obtained from the sample. Thus, mass spectrum profiles are correlated in the claimed method rather than biopolymers. The identification of a peptide by comparison of its mass spectrum profile with mass spectrum profiles of known peptides is a well known practice in the art.

C. The Examiner alleges that the term "particularly" renders claims 4 and 5 indefinite because the claims include elements not actually disclosed (those encompassed by "or the like") thereby rendering the scope of the claims unascertainable.

Claims 4 and 5 have been cancelled herein. None of the remaining pending claims recite the term "particularly".

D. The Examiner alleges that claim 7 is not recited in the proper Markush format. Therein it is not clear as to what "at least

one of the group consisting of" refers.

Claim 7 has been cancelled herein. Pending claim 38 recites Markush language in the proper format.

E. The Examiner alleges that the phrase "at least one analyte thereof" as recited in claims 3-9, 18-28 and 33-35 renders the claims vague and indefinite because it is unclear as to what the phrase is intended to define.

Claims 3-9, 18-28 and 33-35 have been cancelled herein. None of the remaining pending claims recites the phrase "at least one analyte thereof".

F. The Examiner alleges that the term "including" as recited in claims 18, 25 and 33-35 renders the claims vague and indefinite because the term is not clearly defined in the composition/biopolymer of the instant application.

Claims 18, 25, and 33-35 have been cancelled herein. None of the remaining pending claims recites the term "including".

The Examiner alleges that the claims are further unclear because "SEQ ID NO:1" has not been set forth in the claims.

New claims 36-43 clearly recite that the biopolymer marker of the invention is the biopolymer marker consisting of SEQ ID NO:1.

G. The Examiner alleges that the term "regulation" in claim 35 is a relative term which renders the claim indefinite. The term "regulation" is not defined by the claim, the specification does

not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to how the measurement of the biopolymer marker will further serve to control the absence and/or presence of the aforementioned biopolymer marker or analyte thereof. It is suggested by the Examiner that the claim merely recite detection of the biopolymer.

Claim 35 has been cancelled herein. None of the remaining pending claims recite the term "regulation".

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that all of the rejections under 35 U.S.C. 112, second paragraph be withdrawn.

Rejection under 35 USC 101

Claims 3-9, 18-28 and 33-35, as presented on November 18, 2002, stand rejected under 35 USC 101 because the claimed invention allegedly is not supported by a either a specific, substantial, credible or asserted utility or a well-established utility.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a well-established utility.

It has been established that where an applicant has specifically asserted that an invention has a particular utility,

the assertion cannot be simply dismissed by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP 2107.02 III B).

The claims have been amended to recite that the biopolymer marker consisting of SEQ ID NO:1 evidences a link to myocardial infarction.

An objective of the instant invention is to evaluate samples containing a plurality of biopolymer markers for the presence of disease-specific markers which evidence a link to a specific disease state (see the instant specification as originally filed at page 17, lines 11-14). According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 1). Applicants respectfully assert that the instant specification fully supports a connection and/or an association of the claimed biopolymer marker (SEQ ID NO:1) with myocardial infarction. The claimed biopolymer marker (SEQ ID NO:1) was identified as related to myocardial infarction by carrying out the protocols disclosed in the specification (see page 27, line 17 to page 28, line 2 of the instant specification as originally filed). The data presented in Figure 1 clearly evidences that the claimed biopolymer marker (SEQ ID NO:1) was found to be present in patients having myocardial infarction. The figure attached to

the declaration filed herewith shows side-by-side (for easy comparison) mass spectrometric profiles; the upper profile obtained from the sera of a patient having myocardial infarction (MI) and the lower profile obtained from the sera (NHS, normal human sera) of a patient determined to be in a normal physiological state with regard to myocardial infarction. This profile comparison clearly evidences the presence of the 1562 dalton marker (SEQ ID NO:1) in myocardial infarction and the absence of such marker in a normal physiological state. Thus, the biopolymer marker of SEQ ID NO:1 is determined to be linked and/or associated with myocardial infarction.

Thus, Applicants assert that SEQ ID NO:1 is useful for diagnosis and treatment of myocardial infarction since it was found to evidence a link to myocardial infarction (an "asserted" utility). This asserted utility is supported by data derived from the working examples (Figures 1 and 2), which shows that the claimed peptide is found in the serum of patients having myocardial infarction.

Accordingly, Applicants respectfully submit that it is improper for the Examiner to simply dismiss the evidence of the utility of the claimed biopolymer marker as presented by the instant specification and maintain that the claimed marker has no utility.

Furthermore, the Examiner is reminded that an Applicant's

assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants above assertion regarding the use of the claimed biopolymer marker (SEQ ID NO:1).

Furthermore, Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-10; page 17, lines 11-14; page 27, line 17 to page 28, line 2; and Figures 1 and 2).

The claimed biopolymer marker (SEQ ID NO:1) does not evidence a link to a myriad of unspecified diseases but rather evidences a link to a specific disease, myocardial infarction(as shown in Figure 1), thus the invention has a specific utility.

It is common practice in the art to compare protein expression in a disease state to protein expression in a normal physiological and to associate proteins expressed in the disease state and not in the normal state with the disease state; for example, see attached abstract of Gunnersen et al. (PNAS USA 89(24):11949-11953 1992; reference 2). Gunnersen et al. identified expression of a 42kDa ATP binding protein (glutamine synthetase) in the cerebrospinal fluid of patients having Alzheimer's disease but did not observe the protein in the cerebrospinal fluid from normal

patients or other neurological controls. From this observation, Gunnersen et al. suggested that the protein may be a useful diagnostic marker for Alzheimer's disease.

Furthermore, it has been settled that an applicant is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP 2164.07 I C).

The disclosure establishes that the claimed biopolymer marker (SEQ ID NO:1) is found in patients having myocardial infarction but is not found in normal patients. Since it is common in the art to associate proteins differentially expressed from normal with disease, one of skill in the art would recognize that the claimed biopolymer marker (SEQ ID NO:1) is a potential marker for the disease condition, i.e. myocardial infarction. Thus, the presence of the claimed biopolymer marker (SEQ ID NO:1) in a disease state, i.e. myocardial infarction and the absence of the claimed biopolymer marker (SEQ ID NO:1) in a normal physiological state is enough information to label a peptide a "marker" for the disease condition (myocardial infarction), no additional validation or further research is necessary.

Accordingly, Applicants respectfully contend that one of skill

in the art would believe, based upon the information in the specification in light of the knowledge in the prior art, that the claimed biopolymer marker (SEQ ID NO:1) is more likely than not to be a marker of myocardial infarction and therefore has specific utility.

Additionally, if an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

Advances in diagnosis and treatment of heart disease are highly desirable considering that mortality and morbidity due to heart disease are increasing world-wide. Thus, advances in diagnosis and treatment of myocardial infarction would greatly benefit a population which is susceptible to the development of heart disease. The claimed biopolymer marker (SEQ ID NO:1) represents an advance in research regarding heart disease; a "real-world" use benefitting the public, which satisfies the precedent set in *Nelson*. Thus, the claimed biopolymer marker (SEQ ID NO:1) additionally has a substantial utility based upon a "real-world" use.

When considering practical utility ("real-world" utility) relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses (*Nelson v. Bowler and*

Crossley 206 USPQ 881).

The instant specification suggests that the claimed biopolymer marker (SEQ ID NO:1) is useful for diagnostics and/or therapeutics of myocardial infarction since it was found to be present in myocardial infarction and absent in a normal physiological state. Applicants respectfully submit that the observed differential expression is enough evidence such that one of ordinary skill in the art would be reasonably certain of the practical utility of the claimed biopolymer marker (useful for diagnostics and/or therapeutics of myocardial infarction).

Although the Examiner should regard Applicants' statement of asserted utility sufficient to satisfy the requirements of 35 USC 101, the Examiner lists several reasons which allegedly support her argument that the claimed invention has no utility.

The Examiner asserts that the specification states that the claimed sequence (SEQ ID NO:1) was highly expressed in congestive heart failure, but undetectable in other tested disease related to Syndrome X, such as overt diabetes and kidney failure (see page 16, lines 9-18 and page 26, line 20 to page 27, line 2).

Applicants respectfully assert that this statement made by the Examiner is incorrect.

Page 16, lines 9-18 of the instant specification indicate that the next stages of the Syndrome X continuum lead to overt diabetes,

kidney failure, and heart failure, with the possibility of stroke and heart attack at any time. Contrary to the Examiner's assertion, this paragraph makes no mention of SEQ ID NO:1 or its detection in any disease state.

Page 26, line 20 to page 27, line 2 of the instant specification indicates that serum samples from patients suffering from a variety of disease states were analyzed using one or more protein chip surfaces and the profiles were analyzed to discern notable sequences which were deemed in some way evidentiary of at least one disease state. Again, contrary to the Examiner's assertion, this paragraph makes no mention of SEQ ID NO:1 or its detection in any disease state. Furthermore, the instant specification at no point discloses that SEQ ID NO:1 is undetectable in other tested disease states related to Syndrome X, such as overt diabetes and kidney failure.

Thus, since the instant application does not disclose that the claimed sequence was undetectable in tested disease related to Syndrome X, it can not be contradictory to the information presented in the patents cited by the Examiner (US Patent 5,849,297, US Patent 6,221,657 and US Patent 6,268,485).

The Examiner continues by asserting that this (data of the instant invention) is contradictory to information presented in the prior art regarding the utility of the same sequence, namely SEQ

ID NO:1. US Patent 5,849,297, US Patent 6,221,657 and US Patent 6,268,485 teach utility in myocardial ischemia, frostbite, burns (column 7, lines 28-29), glomerulonehphritis, haemolyic anemia, myasthenia gravis, and type II collagen induced arthritis (column 7, lines 34-35). The Examiner asserts that these results do not support Applicants' asserted use of the claimed methods for detection of any disorder, particularly myocardial infarction/congestive heart failure.

Apparently, the Examiner believes that the proteins and methods disclosed in the cited patents (US Patent 5,849,297, US Patent 6,221,657 and US Patent 6,268,485) are analogous to the proteins and methods of the instant application.

The cited US patents and the instant application are not drawn to the same peptides. For example, in US Patent 5,849,297 (Harrison et al.) SEQ ID NO:1 is the sequence of a human C3 complement protein having 1663 amino acid residues. The SEQ ID NO:1 of the instant invention is a peptide fragment of a human C3 complement protein consisting of 13 amino acid residues. The 13 amino acid SEQ ID NO:1 of the instant invention is identical to a portion of the sequence disclosed by Harrison et al. However, the claims clearly recite that the biopolymer marker of the instant invention is the biopolymer marker consisting of SEQ ID NO:1. Since the phrase "consisting of" is closed language and excludes any element, step

or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claims now encompass only this specific peptide (SEQ ID NO:1, 13 amino acid residues in length). Thus, the protein of Harrison et al. is excluded from the scope of the remaining pending claims of the instant invention.

Additionally, the methods disclosed by the cited US Patents are not analogous to the methods disclosed in the instant application. The cited US patents disclose a method of modifying a native complement protein such that formation of a stable C3 convertase is possible. A stable C3 convertase will function to deplete complement proteins and thus is therapeutically useful in immunologically mediated disorders. The instant application discloses a method for identifying differentially expressed proteins (between disease a state and a normal state) which can be considered markers for a disease condition and does not disclose modification of proteins or treatment of any disease.

Thus, contrary to the Examiner's assertion, the results of the experiments disclosed in the cited US patents are unrelated to and thus are in no way contradictory to the results of the experiments disclosed in the instant application.

In conclusion, based upon all of the above arguments, Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed

biopolymer marker (SEQ ID NO:1) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejections under 35 USC 112, first paragraph

Claims 3-9, 18-28 and 33-35, as presented on November 18, 2002, stand rejected under 35 USC 112, first paragraph. Specifically the Examiner asserts that since the claimed invention is not supported by a specific, substantial or credible asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

It has been established by prior arguments in the instant Response that the claimed invention has both a specific and a well established utility. Therefore, Applicants respectfully request that the Examiner now withdraw the rejection under 35 USC 112, first paragraph which was based upon the rejection under 35 USC 101.

Claims 3-9 and 35, as presented on November 18, 2002, stand further rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claims contain subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner asserts that claims 3-9 and 35 are broadly drawn to methods of determining the presence or absence of at least one disease state by analyzing a biological sample obtained from a patient to identify the biopolymer marker sequence consisting of sequence identification NO:1. The specification only sets forth myocardial infarction/congestive heart failure without any control comparison therefore no disease state detection has been presented. The Examiner further asserts that the results set forth in the specification for example in Figure 1 are not clearly indicative of at least one disease state because no control sample analysis is presented by way of example.

In response to the Examiner's assertions, Applicants herein provide the attached Declaration (and figure) under 37 CFR 1.132. The figure attached to the declaration shows side-by-side (for easy comparison) mass spectrometric profiles; the upper profile obtained from the sera of a patient having myocardial infarction (MI) and the lower profile obtained from the sera (NHS, normal human sera) of a patient determined to be in a normal physiological state with regard to myocardial infarction. This profile comparison clearly evidences the presence of the 1562 dalton marker (SEQ ID NO:1) in

myocardial infarction and the absence of such marker in a normal physiological state. Thus, the biopolymer marker of SEQ ID NO:1 is determined to be linked and/or associated with myocardial infarction.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

The instant specification and the declaration attached herein provide evidence showing that the claimed sequence (SEQ ID NO:1) can be a marker for myocardial infarction because it is present in this disease and absent in healthy patients.

The data presented in Figure 1 discloses that the claimed biopolymer marker (SEQ ID NO:1) is found in myocardial infarction, thus it can reasonably predicted that such biopolymer (SEQ ID NO:1) is linked to myocardial infarction.

As discussed above in the section regarding 35 USC 101, it is common practice in the art to compare protein expression in a disease state to protein expression in a normal physiological and

to associate proteins expressed in the disease state and not in the normal state with the disease state. One of ordinary skill in the art would recognize the results of the experiments described herein to follow this scenario.

Thus, Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed biopolymer marker (SEQ ID NO:1) is linked and/or associated with myocardial infarction.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner makes a series of assertions regarding the enablement of subject matter which is not claimed, including the following:

The specification does not enable one of ordinary skill in the art to definitively assess the incidence or further distinguish between any and all diseases other than congestive heart failure in a single test sample. There is no disclosure enabling the use of the biopolymer marker with regard to regulating the presence or

absence of said sequence. Applicants have not set forth any supporting evidence that suggests that any of the sequences (SEQ ID NO:1) are unique markers for myocardial infarction/congestive heart failure and all other possible disease states.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material which is not claimed. The pending claims do not recite any methods which definitively assess the incidence of myocardial infarction or any other disease state. Furthermore, the pending claims do not recite any disease states other than myocardial infarction, nor do the pending claims recite identification of therapeutic avenues or methods of regulating the sequence or a disease state. Thus, no teachings regarding these issues are necessary in order to provide evidence for enablement of the pending claims.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Applicants assert that SEQ ID NO:1 is linked to myocardial infarction, however, do not claim that SEQ ID NO:1 is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed SEQ ID NO:1, a fragment of complement protein C3, is related to myocardial infarction, it does recognize that the pathogenesis of this heart condition involves the activation of complement (see attached abstract of Muscari et al. European Heart Journal 21(13):1081-1090 2000; reference 3). Furthermore, it is known that elevated complement component C3 is a risk factor for myocardial infarction (see Muscari et al; reference 3). When one of ordinary skill in the art observes the presence of the claimed biopolymer marker (SEQ ID NO:1) in myocardial infarction patients and the absence of such marker in healthy patients; one of skill in the art will connect this biopolymer (SEQ ID NO:1) with potential diagnostics and/or therapeutics of myocardial infarction.

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed sequence (SEQ ID NO:1) and myocardial infarction and that this link connotes the use of the claimed sequence (SEQ ID NO:1) in potential diagnostics and/or therapeutics for myocardial infarction, the requirement of "how to use" under 35 USC 112, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of

ordinary skill in the art would find the suggestion of a link between the claimed sequence (SEQ ID NO:1) and myocardial infarction to be reasonable.

At page 27, line 17 to page 28, line 2 of the instant specification as originally filed, SEQ ID NO:1 is identified as a fragment of complement component C3. It has previously been shown that inflammatory mechanisms are involved in myocardial infarction(see Muscari et al., reference 3). Furthermore, the serum level of complement component C3 is known to be a indicator of the risk of myocardial infarction (see Muscari et al., reference 3). One of skill in the art, considering that inflammation is involved in myocardial infarction , upon observation of the presence of the claimed sequence (SEQ ID NO:1) in myocardial infarction along with its corresponding absence in healthy patients, would find it reasonable to believe that the claimed sequence (SEQ ID NO:1) is related to myocardial infarction.

Therefore, one of ordinary skill in the art would recognize the linkage of SEQ ID NO:1 with myocardial infarction and thus would also find the suggestion of SEQ ID NO:1 as a marker for myocardial infarction entirely reasonable.

The Examiner cites two articles; Tascilar *et al.* (see attached abstract, Annals of Oncology 10, Supplement 4:S107-S110 1999; reference 4) and Tockman *et al.* (see attached abstract, Cancer

Research 52:2711s-2718s 1992; reference 5) which are allegedly relevant to the instant invention.

According to the Examiner, Tascilar *et al.* is an article published in an oncogenic journal reporting on diagnostic methods in the realm of disease states. The Examiner appears to have drawn a direct parallel between the diagnostic methods reported by Tascilar *et al.* and the diagnostic methods of the instant invention. The Examiner then cites two fragmented quotations from Tascilar *et al.* "...these tests should be interpreted with caution..." and "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently". The Examiner appears to be commenting on the predictability of molecular-based assays.

Applicants respectfully disagree with the Examiner's reliance on the article by Tascilar et al.

Applicants assert that the claimed peptide (SEQ ID NO:1) is linked to myocardial infarction ; a statement which is enabled by the description of methods as set forth in the specification and by data presented in Figure 1 and in the attached declaration. Thus, applicants respectfully submit that the claimed method involves a simple observation of the presence of SEQ ID NO:1 and does not require any other evaluation of genetic changes in the organism in which the sequence is observed.

Furthermore, the study of Tascilar et al. is concerned with the evaluation of samples for genetic mutations (K-ras and p53 mutations) for early detection of pancreatic cancer (see attached abstract of Tascilar et al. Annals of Oncology 10, Supplement 4:S107-S110 1999; reference 4). It appears that Tascilar et al. suggest that protein markers may be useful for early detection of pancreatic cancer; however there does not seem to be any other reference to protein markers, thus the study of the instant inventors (drawn to protein markers and not to genetic markers) is not analogous to the study of Tascilar et al.

Accordingly, Applicants respectfully submit that the Tascilar *et al.* article is not relevant to the instant invention.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992; reference 5) which is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and

confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. According to the Examiner, Tockman *et al* reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life experience within a population with a disease or disorder are highly speculative and unpredictable.

Tockman *et al* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants also respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman *et al* article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for myocardial infarction. Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345)

cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any "criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a

link between the claimed biopolymer marker (SEQ ID NO:1) and myocardial infarction.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05)

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

In conclusion, Applicants claim that the presence of the claimed biopolymer marker (SEQ ID NO:1) in myocardial infarction patients and the corresponding absence of such marker (SEQ ID NO:1) in healthy patients evidences a link between the claimed biopolymer marker (SEQ ID NO:1) and myocardial infarction; a statement which is enabled by the instant specification, as evidenced by the

arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:1)and myocardial infarction and would further recognize how to use the claimed biopolymer marker (SEQ ID NO:1) as a marker for myocardial infarction. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

Rejection under 35 USC 102(b)

Claim 35, as presented on November 18, 2002, stands rejected under 35 USC 102(b) as allegedly being anticipated by Harrison et al. (US Patent 5,849,297).

The Examiner alleges that Harrison et al. disclose biologically active polypeptides comprising therapeutically active polypeptides. See abstract. Applicants sequence identification number 1 is disclosed as sequence identification number 1 in the patent to Harrison et al. The Examiner alleges that therein the claimed sequence is taught. Harrison et al. further teach the utility of said sequences in disease state detection, evaluation and treatment. See column 6 through 8.

Claim 35 has been cancelled herein. None of the remaining pending claims are drawn to any process for regulating a disease

state or to any process which controls the presence or absence of SEQ ID NO:1.

The SEQ ID NO:1 of Harrison et al. is the sequence of a human C3 complement protein having 1663 amino acid residues. The SEQ ID NO:1 of the instant invention is a peptide fragment of a human C3 complement protein consisting of 13 amino acid residues. The 13 amino acid SEQ ID NO:1 of the instant invention is identical to a portion of the sequence disclosed by Harrison et al. However, the remaining pending claims clearly recite that the biopolymer marker of the instant invention is the biopolymer marker consisting of SEQ ID NO:1. Since the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claims now encompass only this specific peptide (SEQ ID NO:1, 13 amino acid residues in length). Thus, the protein of Harrison et al. is excluded from the scope of the remaining pending claims of the instant invention.

Accordingly, Applicants respectfully submit that the claims, as instantly presented, now distinguish over the sequences taught by Harrison et al. and respectfully request that this rejection under 35 USC 102(b) be withdrawn.

Rejection under 35 USC 102(a)(e)

Claim 35, as presented on November 18, 2002, stands rejected

under 35 USC 102(a)(e) as allegedly being anticipated by Harrison et al. (US Patent 6,221,657).

The Examiner alleges that Harrison et al. disclose biologically active polypeptides comprising therapeutically active polypeptides. See abstract. Applicants sequence identification number 1 is disclosed as sequence identification number 1 in the patent to Harrison et al. The Examiner alleges that therein the claimed sequence is taught. Harrison et al. further teach the utility of said sequences in disease state detection, evaluation and treatment. See column 6 through 8.

Claim 35 has been cancelled herein. None of the remaining pending claims are drawn to any process for regulating a disease state or to any process which controls the presence or absence of SEQ ID NO:1.

The SEQ ID NO:1 of Harrison et al. is the sequence of a human C3 complement protein having 1663 amino acid residues. The SEQ ID NO:1 of the instant invention is a peptide fragment of a human C3 complement protein consisting of 13 amino acid residues. The 13 amino acid SEQ ID NO:1 of the instant invention is identical to a portion of the sequence disclosed by Harrison et al. However, the remaining pending claims clearly recite that the biopolymer marker of the instant invention is the biopolymer marker consisting of SEQ ID NO:1. Since the phrase "consisting of" is closed language and

excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claims now encompass only this specific peptide (SEQ ID NO:1, 13 amino acid residues in length). Thus, the protein of Harrison et al. is excluded from the scope of the remaining pending claims of the instant invention.

Accordingly, Applicants respectfully submit that the claims, as instantly presented, now distinguish over the sequences taught by Harrison et al. and respectfully request that this rejection under 35 USC 102(b) be withdrawn.

Rejection under 35 USC 102(e)

Claim 35, as presented on November 18, 2002, stands rejected under 35 USC 102(e) as allegedly being anticipated by Farries et al. (US Patent 6,268,485).

The Examiner alleges that Farries et al. disclose native pathway proteins, which form a down-regulation resistant C3 convertase. The proteins are modified human C3 protein. Applicants sequence identification number is disclosed as sequence identification number 22 in the patent to Farries et al. The Examiner alleges that therein the claimed sequence is taught. Farries et al. further teach the utility of said sequences in disease state detection, evaluation and treatment. See column 6 through 8.

Claim 35 has been cancelled herein. None of the remaining pending claims are drawn to any process for regulating a disease state or to any process which controls the presence or absence of SEQ ID NO:1.

The SEQ ID NO:22 of Farries et al. is the sequence of a human C3 complement protein having 1663 amino acid residues. The SEQ ID NO:1 of the instant invention is a peptide fragment of a human C3 complement protein consisting of 13 amino acid residues. The 13 amino acid SEQ ID NO:1 of the instant invention is identical to a portion of the sequence disclosed by Farries et al. However, the remaining pending claims clearly recite that the biopolymer marker of the instant invention is the biopolymer marker consisting of SEQ ID NO:1. Since the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claims now encompass only this specific peptide (SEQ ID NO:1, 13 amino acid residues in length). Thus, the protein of Farries et al. is excluded from the scope of the remaining pending claims of the instant invention.

Accordingly, Applicants respectfully submit that the claims, as instantly presented, now distinguish over the sequences taught by Farries et al. and respectfully request that this rejection under 35 USC 102(b) be withdrawn.

Rejection under 35 USC 103(a)

Claims 18-28, 33 and 34, as presented on November 18, 2002, stand rejected under 35 USC 103(a) as allegedly being unpatentable over Harrison et al. (US Patent 5,849,297), Harrison et al. (US Patent 6,221,657) or Farries et al. (US Patent 6,268,485) in view of Foster et al. (US Patent 4,444,879).

The Examiner notes that the teachings of Harrison et al. (US Patent 5,849,297), Harrison et al. (US Patent 6,221,657) and Farries et al. (US Patent 6,268,485) are set forth in the sections concerning rejections under 35 USC 102 and further notes that these references fail to teach the assay as a kit.

The Examiner asserts that kits are well known embodiments for assay reagents. Foster et al. (US Patent 4,444,879) describe one example. In Foster et al. kits including the reactant reagents, a microplate, positive controls, negative controls, standards, and instructions are taught (see Figure 6, and column 15, lines 10-34).

The Examiner asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicants' invention to take the detection assay as taught by Harrison et al. (US Patent 5,849,297), Harrison et al. (US Patent 6,221,657) or Farries et al. (US Patent 6,268,485) and format them into a kit because Foster et al. teach that it is convenient to do so and one can enhance sensitivity of a method by providing

reagents as a kit. Further, the reagents in a kit are available in pre-measured amounts, which eliminates the variability that can occur when performing the assay.

Applicants respectfully disagree with the Examiner's determination that the claimed subject matter is obvious.

Claims 18-28, 33 and 34 have been cancelled herein. New claims 41-43 are drawn to kits.

In order for an Examiner to establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations.

It has been established in the above sections regarding the rejections under 35 USC 102, that the peptide of the claimed invention (SEQ ID NO:1) is distinguishable over the protein disclosed by Harrison et al. (US Patent 5,849,297), Harrison et al. (US Patent 6,221,657) and/or Farries et al. (US Patent 6,268,485). Additionally, Foster et al. (US Patent 4,444,879)do not disclose any complement C3 peptides and/or proteins. Thus, the prior art relied on by the Examiner to support the rejection of claims under 35 USC 103(a)does not teach or suggest all of the claim limitations. Furthermore, one of ordinary skill in the art would not be able to create a kit as taught by the instant invention without access to the data collected by the instant inventors regarding the biopolymer marker (SEQ ID NO:1) of the invention;

i.e. one of ordinary skill in the art would not know how to select the exact peptide of SEQ ID NO:1 from the amino acid sequence of complement C3 protein.

In light of all of the above remarks, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and further contend that a biologist of ordinary skill in the art, having the references (Harrison et al. (US Patent 5,849,297), Harrison et al. (US Patent 6,221,657) Farries et al. (US Patent 6,268,485) and Foster et al. (US Patent 4,444,879))in front of him/her would not have the information and motivation necessary to arrive at Applicants' invention.

Thus, it is respectfully submitted that the combination of Harrison et al. (US Patent 5,849,297), Harrison et al. (US Patent 6,221,657) or Farries et al. (US Patent 6,268,485) and Foster et al. (US Patent 4,444,879)fails to reasonably teach or suggest to one of ordinary skill in the art the elements of Applicants' kits as specifically set forth in claims 41-43 as presented herein.

Accordingly, Applicants respectfully submit that the claimed kit distinguishes over the prior art and respectfully request that this rejection under 35 USC 103(a) now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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